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14. ABSTRACT

This study consists of a 14-week, two parallel group, randomized placebo controlled trial to evaluate the efficacy and tolerability of the alpha-1 adrenergic antagonist, prazosin, for reducing trauma nightmares and sleep disturbance and improving global function and sense of well-being, in 210 OIF and OEF combat-exposed returnees with PTSD and persistent trauma-related nightmares and disrupted sleep. A secondary aim is to assess efficacy of prazosin for reducing total PTSD symptoms, reducing symptoms of depression, improving quality of life, and reducing alcohol craving.

15. SUBJECT TERMS
PTSD, prazosin, trauma nightmares, sleep

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Introduction:

The objective of this randomized controlled trial (RCT) has been to evaluate the efficacy and tolerability of the alpha-1 adrenergic antagonist prazosin compared to placebo for combat stress-related nightmares, sleep disturbance, and global function in combat trauma-exposed Service Members who are in garrison at Joint Base Lewis McChord (JBLM). The secondary objectives of this trial are to assess the efficacy of prazosin for reducing total PTSD symptoms, reducing symptoms of depression and improving quality of life.

Active duty soldiers who have experienced combat in OIF/OEF/OND and who have persistent combat stress-related nightmares and sleep disturbance in the context of combat trauma PTSD have been enrolled in the study. Participants undergo a flexible dose titration period followed by optimal dose treatment for a total of 15 weeks including the titration period. Primary and secondary outcome measures assess nightmares, sleep disturbance, PTSD severity by total CAPS score, depression, global function, and quality of life and are administered every four weeks (weeks 7, 11 and 15).

Body:

We have successfully launched and brought to a halfway point preplanned interim analysis what, to our knowledge, is the first ever medication randomized controlled trial for PTSD (or any other behavioral disorder) performed in US active duty combat experienced Service Members. Our active outreach approach to recruitment across JBLM has successfully attracted volunteers for research participation, and also has provided support to the Psychiatry Service mission at Madigan Army Medical Center (MAMC) and JBLM.

Key Research Accomplishments

- We performed a planned "halfway" interim analysis on the first 67 randomized subjects. 54 had at least one full behavioral outcome (the evaluable sample) and 49 completed the entire 15-week trial. An Intent to treat linear mixed effects models analysis utilizing data from all randomized subjects has been performed.

Reportable Outcomes

Prazosin was significantly superior to placebo for all three primary outcome measures. CAPS B2 nightmare score decrease from baseline to end point was 3.1 ± 0.3 (mean ± SE) in the prazosin group vs. 1.2 ± 0.3 in the placebo group (difference in change from baseline $p < 0.001$, 95%, CI for difference in change from baseline [1.0, 2.8]). PSQI decrease from baseline to endpoint was 5.6 ± 0.7 in the prazosin group vs. 2.8 ± 0.6 in the placebo group (difference in change from baseline $p=0.004$, 95% CI [0.9, 4.6]) adjusted per cent CGIC responders ("markedly" or "moderately" improved for prazosin subjects was 64% (95% CI [44%, 79%] compared to 26% (95% CI [14%, 44%] for placebo subjects (difference in per cent responders $p < 0.001$, odds ratio 4.9, 95% CI [1.9, 12.3]. Prazosin was well tolerated.These data are presented graphically in the attached poster presented 3 December 2012 at the American College of Neuropsychopharmacology Annual Meeting. A manuscript describing these results is under consideration by the American Journal of Psychiatry.

Conclusions

After review of the interim data analysis by the MAMC data monitoring officer and IRB, they concluded that randomization should be halted because of clear efficacy and clinical availability of prazosin. MAMC Psychiatry has requested that VA study personnel continue to follow completed subjects for ongoing care. This will assist the MAMC clinical care mission and also enable obtaining long-term follow-up (open label) data through June 2013 on service members initially randomized to and continued on open label prazosin, as well as on service members initially randomized to placebo and switched to open label prazosin for persistent PTSD

symptoms at end of double blind. We also plan a number of additional data analyses and manuscript preparation during the next 6 months. These include differential effects on prazosin response of a maintenance antidepressant, an analysis of concomitant non-psychotropic medications and medical conditions, and others.

References (for background)

Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbances in combat veterans with posttraumatic stress disorder. *Biol Psychiatry* 61:928-934, 2007.

Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003 February; 160(2):371-3.

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Appendices

N/A

Supporting Data

Pending

A Placebo-Controlled Augmentation Trial of Prazosin for Combat Trauma PTSD

PI: Murray A. Raskind, MD **Org:** VA Puget Sound – Seattle Institute for Biomedical & Clinical Research

Problem, Hypothesis and Military Relevance

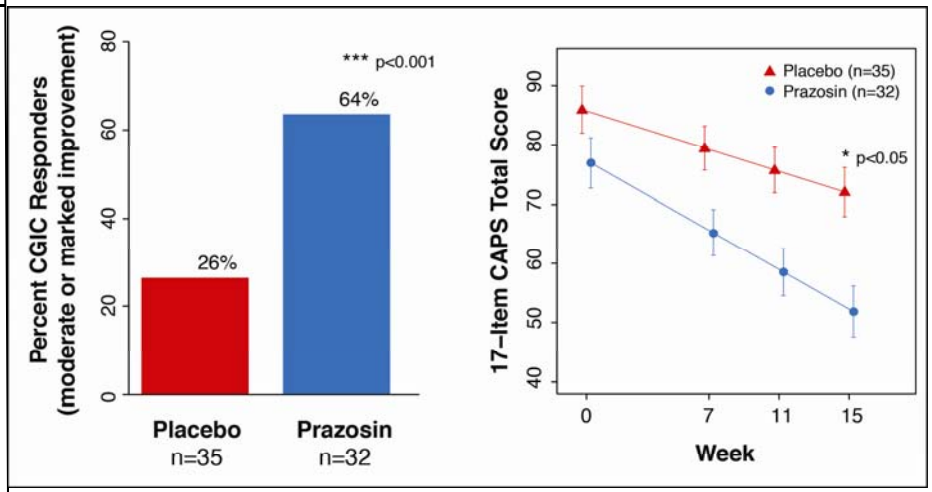
- **Problem**: Preliminary data in Vietnam Veterans suggested prazosin efficacy for PTSD nightmare, sleep disruption, global status, and overall PTSD.
- **Hypothesis**: Prazosin is more effective than placebo for PTSD nighttime symptoms, function, and overall PTSD in active duty soldiers returned from combat deployments to OEF/OIF/OND.
- Outcome measures are: CAPS, B-2 nightmare item, Pittsburgh Sleep Quality Index (PSQI), Clinical Global Impression of Change (CGI) anchored to function, and 17 item CAPS total score.
- **Military Relevance**: PTSD is a common cause of distress and disability in service members and Veterans..

Timeline and Total Cost

Activities FY:	1	2	3	4	5
Start-up activities					
Recruit, enroll, and perform all study procedures; double data entry, data cleaning. Prelim data analyses					
Long term open label clinical follow-up of randomized service members. Collection of long term data and secondary data analyses, manuscript preparation					
Total Budget (1,776,722)	355K	355K	355K	355K	355K

Accomplishments

We have completed the efficacy phase of this study. Prazosin was significantly superior to placebo for all primary outcome measures. CAPS B2 nightmare score decrease from baseline to end point was 3.1 ± 0.3 (mean ± SE) in the prazosin group vs. 1.2 ± 0.3 in the placebo group (difference in change from baseline $p < 0.001$, 95%, CI for difference in change from baseline [1.0, 2.8]). PSQI decrease from baseline to endpoint was 5.6 ± 0.7 in the prazosin group vs. 2.8 ± 0.6 in the placebo group (difference in change from baseline $p=0.004$, 95% CI [0.9, 4.6]). Per cent CGIC responders ("markedly" or "moderately" improved) for prazosin subjects was 64% (95% CI [44%, 79%] compared to 26% (95% CI [14%, 44%] for placebo subjects (difference in per cent responders $p < 0.001$, odds ratio 4.9, 95% CI [1.9, 12.3].



Prazosin is effective for overall PTSD (17 items CAPS) and Clinical Global Impression of Change (anchored to function at work and home) in active duty soldiers.

A Randomized Controlled Trial of Prazosin for Combat Trauma PTSD with Nightmares in Active Duty Soldiers Returned from Iraq and Afghanistan

Murray Raskind, MD; Elaine Peskind, MD; COL (RET) Kris Peterson, MD; COL Dallas Homas, MD; Kimberly Hart, PA-C; David Hoff, PA-C; Tammy Williams, LCSW; Hollie Holmes, BA

VA Northwest Network Mental Illness Research, Education and Clinical Center (MIRECC); Madigan Health Care System, Joint Base Lewis McChord, Washington

BACKGROUND

• Prazosin is a generically available (inexpensive) alpha-1 adrenoreceptor antagonist that easily enters the brain and reduces excessive norarenergic-mediated arousal.

• Prazosin at bedtime has been demonstrated effective for PTSD nightmares and sleep disruption in Vietnam Veterans[1] and civilians.[2]

QUESTIONS

• Is prazosin effective for PTSD with prominent trauma nightmares in active duty Soldiers returned from combat in Iraq/Afghanistan?

• Is twice daily prazosin effective for total PTSD symptoms in these Soldiers?*
- Midmorning dose titrated to maximum 5 mg
- Bedtime dose titrated to maximum 20 mg

• Is this prazosin dosing regimen well tolerated by active duty Soldiers engaged in physically and mentally demanding training?

* Female soldiers maximum dose 2mg AM and 10mg HS

METHODS

• Soldiers randomized to prazosin or placebo for 15 weeks (6 week titration, 9 week maintenance dose). Outcome ratings at weeks 7, 11, and 15.

Table 1. Titration Schedule

	AM Dose (1000-1100 hrs)		QHS dose	
	Male Subjects	Female Subjects	Male Subjects	Female Subjects
Week 1 Days 1 and 2 Days 3-7			1 mg 2 mg	1 mg 2 mg
Week 2	1 mg	1 mg	4 mg	2 mg
Week 3	2 mg	1 mg	6 mg	4 mg
Week 4	2 mg	2 mg	10 mg	6 mg
Week 5	5 mg	2 mg	15 mg	10 mg
Week 6	5 mg		20 mg	

Table 2. Demographics

	Prazosin (n=32)	Placebo (n=35)
Age	30 ± 7 years	31 ± 7 years
Male	26 (81%)	31 (89%)
Married (%)	68%	62%
Median rank	E-5 (Sergeant)	E-5 (Sergeant)
Maintenance SSRI	9	12

RESULTS

• 56 of 67 subjects completed at least one rating period, and 46 the entire 15-week study. Data analyzed with linear mixed effects models using data from all 67 randomized subjects.

• Average doses achieved in male soldiers:

Prazosin (mg)

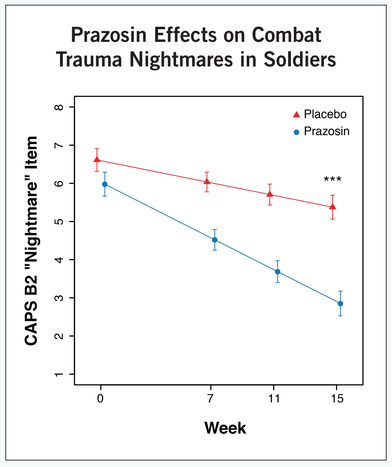
4.0 ± 1.4 midmorning/15.6 ± 6.0 bedtime

Placebo (mg)*

4.8 ± 0.8 midmorning/18.8 ± 3.3 bedtime

*placebo > prazosin, $p < 0.05$

A.



***$p < 0.001$

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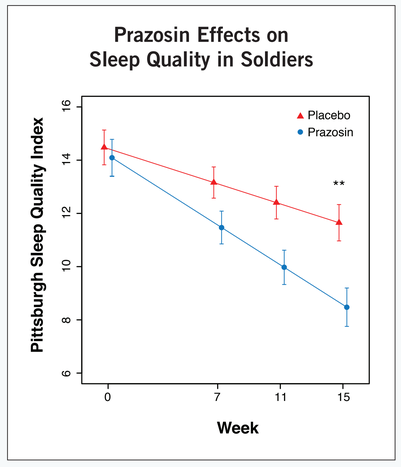

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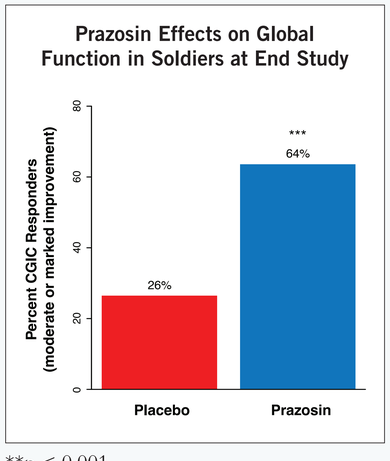

**$p < 0.001$

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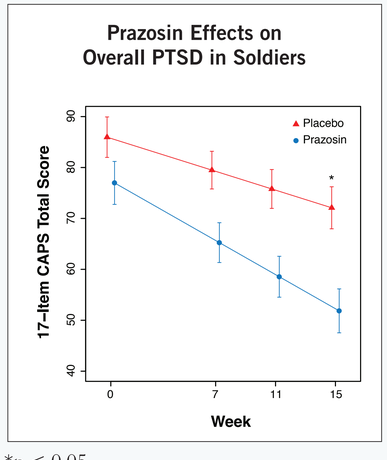

*$p < 0.05$

• Prazosin significantly superior for CAPS hyperarousal cluster and numerically superior for depression ratings (HAM-D, PHQ-9). No drug effect on blood pressure.

ADVERSE EFFECTS

	Prazosin	Placebo
Syncope	1	0
Dizziness	6	6
Drowsiness	1	2
Depressed mood	0	2
Headache	1	7
Nasal congestion	5	2
Nausea	2	5
Palpitations	4	1

CONCLUSIONS

• Prazosin prescribed twice daily at mid-morning and bedtime is an effective and well tolerated treatment for combat trauma nightmares, sleep disturbance, function and overall PTSD in Soldiers returned from Iraq and Afghanistan combat deployment(s).

• Substantial residual PTSD symptoms suggest that adding effective psychotherapy and/or other medications may further enhance efficacy.

REFERENCES

1. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbances in combat veterans with posttraumatic stress disorder. Biol Psychiatry 61:928-934, 2007. PMID: 17069768.

2. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma PTSD: a placebo-controlled study. Biol Psychiatry 63:629-632, 2008.

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